REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following claims.

The claims presently pending before the Examiner are 26-43 and 47-49.

The claims stand rejected under 35 USC § 103 as being unpatentable under 35 USC § 103(a) over Alt, US 5,512,684. This rejection is respectfully traversed.

Applicants respectfully disagree with the Examiner's reasoning, and hereby submit further arguments in support to the non-obviousness of the claims.

The claimed invention recites a process for preparing raloxifene hydrochloride in a pure and crystalline form, compared to those known from the prior art. While it may be true that the process recited in independent claim 26 (and the claims depending thereon) is similar in its initial part to US '684, it differs and distinguishes from the '684 process in the last steps d1) and d2).

The Examiner asserted that US '684 describes all of the steps a)-d) and that US '684 differs from the instant application in the fact that:

- US '684 isolated the crude product 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting it to the desired product (I), while the claimed invention does not isolate (VI);

- the instant application describes the purity of the products in the claimed process.

As regards Applicants' motivation, the Examiner, by referring to *In re Mostovych*, states that the adjustment of conventional working conditions is deemed merely a matter of judicious selection and routine optimization and that it is well within the purview of the skilled artisan to reduce steps in order to achieve the desired product faster and in higher yields.

The Applicants, most respectfully, totally disagree with the Examiner's analysis. First of all, nowhere in US '684 is the step of hydrolysis described comprising both the d1) and d2) operative modalities as claimed herein. Specifically, under the title "DEPROTECTION OF REPROTECTED DIHYDROXYTHIPHENES" at cols. 10 and 11 it is stated that "*Both –COR3 and –SOR3- protected compounds have been deprotected by simple hydrolysis with strong or moderately strong bases.....alkali metal hydroxides may be used for the hydrolysis at temperatures from about the ambient temperature to about 100°C.....The reaction may be also carried out however in any convenient solvent..... such as polyols. ... In case of compounds protected with –COR3 groups, hydrolysis is also readily carried out with acid catalysts.....*".

Therefore, US '684 does not describe the basic characterization of step d), i.e. the subsequent operative modalities d1) and d2) of step d), by suggesting contrarily either the alkali hydrolysis or acid catalyzed hydrolysis.

The section of US '684 identified by the Examiner i.e. the part at col. 11, lines 28-39, is no more than a general indication that certain protective groups can be removed with bases or acids. In other words, col. 11, lines 1-5 or 28-39 of US '684 could at most teach (but that was not needed because any technician already had this knowledge) one of ordinary skill in the art how to carry out the deprotection steps of the process, but not that by properly operating such deprotection steps he could have avoided most of the passages therein.

Furthermore, in Example 6 of US '684, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene is converted into 6-hydroxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene by reacting the 6-acetoxy product with sodium hydroxide in methanol. Subsequently, the solvent was removed under vacuum and the residue dissolved in methanol and extracted twice with diethylether. The aqueous layers were then acidified to pH2-3 and made basic to pH8. The so-obtained basic solution was then extracted several times and after vacuum drying the crude product "*was used in experimentation on crystallization and purification*

procedures and so no precise total purified yield was determined". Chromatographic steps were then carried out.

Therefore, there is no suggestion of the peculiarities of sub-step d1) and the complete absence of the existence of the immediately subsequent sub-step d2) can be found in US '684. The Applicants once again do not understand exactly on what the Examiner's reasoning is based upon, and what is to be considered, in the Examiner's view, the starting point in US '684 that would lead to the claimed invention.

At the end of Example 6, when it comes to the final product to be isolated, Alt '684 consistently adopts a long sequence of steps comprising evaporation under vacuum, different washings, and chromatographic purification. ***Thus, one of ordinary skill in the art, by reading the entirety of US '684, the person of ordinary skill would never have thought of eliminating the crystallization and purification steps that are consistently carried out in US '684, thus leading the person of ordinary skill to believe that these are necessary steps***. Similarly, no motivation, suggestion, or hint can be found in the cited prior art to replace the sequence of these steps, specifically the chromatographic purification, in favor of the much simpler addition of concentrated HCl and washing with the particular mix of solvents of the claimed invention (peculiarities of sub-step d2).

The Examiner ***recognizes*** that Alt, US '416, which has an identical description to Alt US '684, does not disclose the features of the last step of the claimed invention. The two (2) Alt patents do not in any manner serve to complement the information about the production of a di-hydroxy compound starting from a di-methoxy compound (starting compound of the synthesis of the claimed invention). Applicants' last step, as embodied in claim 26, clearly distinguishes over the disclosure of Alt.

Thus, the "*prima facie* obviousness" finding at pages 5-7 of the Office Action, where the Examiner contends that "*The adjustment of particular conventional working conditions ... is deemed merely a matter of ... selection and routine optimization ...*" is ***totally groundless***. However, in the decision *In re Mostovich*, which the Examiner cites, it is required that information necessary for arriving at the invention are "***beneficially taught***" by the prior art, in order to find that the invention is obvious. In the present

situation, there was no teaching in Alt '416 of the steps d1) and d2) which are critical to the claimed invention, and that to afford the obtention of a dramatically improved yield by means of a simplified process. Applicant's respectfully submit that, in their opinion, the cited prior art does not "***beneficially teach***" the limitations of the claimed invention.

The number of possible modifications of a chemical process, be they in terms of reactants, solvents, temperature, catalysts, ..., is essentially infinite, so absent such a "***beneficial teaching***" the skilled artisan, with knowledge of a given process and aimed at improving it, has no idea where to look or what steps to take to reach his goal. In the present case, nowhere in the cited Alt patent is it said, or taught, or even suggested, that the hydrolysis step can be made by sub-step d1) and the subsequent sub-step d-2), thus avoiding the step of vacuum removal of the solvent, the step of extraction and the chromatographic step, to yield the desired product, namely, crystalline raloxifene hydrochloride. Since, the "routine optimization" of In re Mostovich, being absent, a hint in the right direction in US '684, is not even conceivable.

By reading US '684 one of ordinary skill in the art at the time the invention was made would have understood that it is necessary to employ a long sequence of steps, at the end of the complete synthesis process, to isolate the desired product. Nowhere in US '684 would one of ordinary skill have gotten a suggestion to avoid the complicated sequence of steps reported in Example 6 of US '684.

The other point, the fact that Alt '684 does not describe the impurities content of his final product, is presented by the Examiner as of secondary importance, while, in fact, it is crucial. The value of the claimed invention ***resides precisely*** in the fact that it allows the obtention in a simple manner of a highly pure product, so this deficiency in US '684 (which hides the fact that the process in Alt leads to an impure product, that requires a long purification procedure) is extremely important and not simply an afterthought which is only of secondary importance. In fact, it is an ***index of non-obviousness***.

As stated above, the Examiner advances a "*prima facie* obviousness" case citing also the Dorwald reference to add motivation to his reasoning. Specifically, he states at page 7 of the Office Action that, "*Dorwald clearly states that in the design of an organic*

molecule, a synthetic chemist would need to analyze the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity" see page 2 under 1.2 "synthesis design".

It's clear that the citation is a desideratum of any organic chemist when projecting a synthesis of a compound, "ideally" obtained in high yield and purity, but this does not mean that the technical result cannot be worthy of being patentable. The obviousness must be evaluated on the basis of the prior art and the skilled person in the art, and in this case the skilled person would have never achieved the claimed result on the basis of US '684.

The very fact that the Examiner finds motivation for his reasoning in a general citation of what ideally is desired by a chemist, testifies that he is making a hindsight reconstruction of the claimed invention. Applicants are definitely convinced that the Examiner came to his conclusions on the basis of a further hindsight, while it is clear that the skilled person would have had no motivation to achieve the invention on the basis of US '684.

Therefore, in view of the Dorwald reference which is cited to find motivation for the obviousness rejection in view of US '684, it again underscores that the Examiner's obviousness opinion is necessarily based on hindsight. The fact that the deviations from the prior art are an ideal desideratum of any organic chemist is not the standard for a finding of obviousness. Rather, it is exactly the contrary that is true, namely, that ***achieving an ideal desideratum*** in view of the prior art of Alt is ***clear evidence of inventiveness***.

It is respectfully submitted that Applicants have clearly demonstrated that the claimed invention distinguishes over the deficient teachings of the Alt reference and, as such, the rejection has been overcome and should be withdrawn since *prima facie* obviousness has not been established by a preponderance of the evidence.

The issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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